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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/645,706

08/24/2000

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09/03/2008

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EXAMINER

PROUTY, REBECCA E

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

09/03/2008

PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte KEITH V. WOOD, MONIKA G. GRUBER,
YAO ZHUANG, and AILEEN PAGUIO

Appeal 2008-3429
Application 09/645,706
Technology Center 1600

Decided: September 3, 2008

Before DONALD E. ADAMS, LORA M. GREEN, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a synthetic nucleic acid. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Background

“A promoter is a DNA sequence capable of specific initiation of transcription and consists of three general regions” (Spec. 1). The Specification notes that “it is useful to synthetically alter the natural nucleotide sequence encoding a polypeptide to better adapt the polypeptide for alternative applications. A common example is to alter the codon usage frequency of a gene when it is expressed in a foreign host cell” (Spec. 2). The Specification comments that “altering codon usage may, in turn, result in the unintentional introduction into a synthetic nucleic acid molecule of inappropriate transcription regulatory sequences. This may adversely effect transcription, resulting in anomalous expression of the synthetic DNA” (Spec. 2).

Statement of the Case

The Claims

Claims 1, 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-88, and 90-96 are listed in the claims appendix. We will focus on claims 1, 18, and 90, which are representative and read as follows:

1. A first synthetic nucleic acid molecule comprising at least 300 nucleotides of a coding region for a reporter polypeptide which has at least 90% amino acid sequence identity to a reporter polypeptide encoded by a wild type nucleic acid sequence, wherein the codon composition of the first synthetic nucleic acid molecule is different at more than 25% of the codons from that of the wild type nucleic acid sequence and is different than the codon composition of a second synthetic nucleic acid molecule which encodes a reporter polypeptide which has at least 90% amino acid sequence identity to the reporter polypeptide encoded by the wild type nucleic acid sequence, wherein the codons in the

second synthetic nucleic acid molecule that are different than the codons in the wild type nucleic acid sequence are mammalian high usage codons selected to result in the second synthetic nucleic acid molecule having a reduced number of a combination of different mammalian transcription factor binding sequences, and optionally a reduced number of intron splice sites, poly(A) addition sites or prokaryotic 5' noncoding regulatory sequences relative to the wild type nucleic acid sequence, wherein the codons which differ in the first synthetic nucleic acid molecule relative to the second synthetic nucleic acid molecule are mammalian codons selected to result in the first synthetic nucleic acid molecule having a reduced number of a combination of different mammalian transcription factor binding sequences, and optionally a reduced number of intron splice sites, poly(A) addition sites or prokaryotic 5' noncoding regulatory sequences, that are introduced to the second synthetic nucleic acid molecule by selecting the mammalian high usage codons, wherein the mammalian transcription factor binding sequences are those present in a database of transcription factor binding sequences, wherein the wild type nucleic acid sequence encodes chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase, beta-glucuronidase or beta-galactosidase.

18. A synthetic nucleic acid molecule comprising SEQ ID NO:7 (GRver5), SEQ ID NO:8 (GRver6), SEQ ID NO:9 (GRver5.1), or SEQ ID NO:297 (GRver5.1), or a nucleic acid molecule which is capable of hybridizing thereto under high stringency conditions, or the complement of the hybridizable nucleic acid molecule which encodes a luciferase.

90. The first synthetic nucleic acid molecule of claim 1 wherein the mammalian transcription factor binding sequences, intron splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences in the wild

type nucleic acid sequence or the second synthetic nucleic acid sequence are identified with software, wherein the identified intron splice sites are selected from AGGTRAGT, AGGTRAG, GGTRAGT or YNCAGG, the identified poly(A) addition sites have AATAAA, the identified prokaryotic 5' noncoding regulatory sequences are selected from TATAAT, or AGGA or GGAG if a methionine codon is within 12 bases 3' of the AGGA or GGAG, and the identified mammalian transcription factor binding sequences are in a database of transcription factor binding sequences, mutant transcription factor binding sequences and consensus transcription factor binding sequences, and identified under parameters that allow for partial ambiguity with sequences in the database, wherein the codons are selected to reduce the number of identified sequences or sites, and wherein the first synthetic nucleic acid molecule has fewer mammalian transcription factor binding sequences than the second synthetic nucleic acid molecule which has fewer mammalian transcription factor binding sequences than the wild type nucleic acid sequence

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Sherf et al.	US 5,670,356	Sep. 23, 1997
Zolotukhin et al.	US 5,874,304	Feb. 23, 1999
Cornelissen et al.	US 5,952,547	Sep. 14, 1999
Hey et al.	US 6,169,232 B1	Jan. 2, 2001
Donnelly et al.	WO 97/47358	Dec. 18, 1997
Wood et al.	WO 99/14336	Mar. 25, 1999

Weiqing Pan et al., *Vaccine candidate MSP-1 from Plasmodium falciparum: a redesigned 4917 bp polynucleotide enables synthesis and isolation of full-length protein from Escherichia coli and mammalian cells*, 27 NUCLEIC ACIDS RESEARCH 1094-1103 (1999).

Keith V. Wood et al., *Introduction to Beetle Luciferases and their Applications*. 4 J. OF BIOLUMINESCENCE AND CHEMILUMINESCENCE 289-301 (1989).

Keith V. Wood, *The Chemical Mechanism and Evolutionary Development of Beetle Bioluminescence*. 62 PHOTOCHEMISTRY AND PHOTOBIOLOGY 662-673 (1995).

J.W. Hastings, *Biological Diversity, Chemical Mechanisms, and the Evolutionary Origins of Bioluminescent Systems*, 19 J. OF MOLECULAR EVOLUTION 309-321 (1983).

The issues

The rejections as presented by the Examiner are as follows:

- A. Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite (Ans. 7).
- B. Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-33, 35-39, 41-45, 60, 67, 69, 70, 81, 86, 88 and 90-95 stand rejected under 35 U.S.C. § 112, first paragraph as not being enabled for the full scope of the claims (Ans. 9).
- C. Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86, and 90-95 stand rejected under 35 U.S.C. § 103(a), as being obvious over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, and Hey (Ans. 13-14).
- D. Claims 18, 47, 71, 74, 76-78, 80, 82-85, 87, 88, and 96 stand rejected under 35 U.S.C. § 103(a), as being obvious over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey, and Wood (WO 99/14336) (Ans. 18).
- E. Claims 91, 93, and 94 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-50 and 58-60 of copending Application No. 10/314,827.

A. 35 U.S.C. § 112, second paragraph rejection

The Examiner argues that regarding the transcription factor binding sites and the other transcription control elements that “each of them is an open-ended group of sequences which includes many unknown members and many such consensus sequences are defined differently by individual people such that the boundaries of variations which can occur within a sequence are often vague” (Ans. 8). The Examiner further contends that “while many transcription factors and their associated binding sequences are known in the art, new members are being added frequently such that the scope of the claims would change over time and what sequences constitute active variants of even the known sequences is vague and often context dependent” (Ans. 8).

Appellants argue that “that those skilled in the art, even in the absence of Appellant's specification, understand the metes and bounds of the [claimed] phrases” (App. Br. 18). Appellants contend that “one of skill in the art is aware of databases having transcription factor binding sequences” (App. Br. 19). Appellants further state that “each of the recited classes of sequences or sites has a definite property that is recognizable (and testable) by one of skill in the art” (App. Br. 20).

In view of these conflicting positions, we frame the indefiniteness issue before us as follows:

Are the phrases identified by the Examiner in the claims vague and indefinite?

Discussion of 35 U.S.C. § 112, second paragraph rejection

We agree with Appellants that the skilled artisan understands the meaning of each of the claim terms in dispute. We further agree with Appellants that there is no need to limit the claims to a particular set of sequences as suggested by the Examiner (Ans. 23). The tenor of the Examiner's arguments is that while "TRS [transcription regulatory sequences] can be identified using databases and software, and pages 48-50 define a particular set of sequences . . . the claims do not define particular databases and software or particular sequences and the claims are not limited to those used in the specification" (Ans. 22-23). The Examiner doesn't indicate that the claims terms are unclear, vague or otherwise confusing to the ordinary practitioner, just broad. The Examiner is equating the breadth of the claim with indefiniteness; however, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971).

Further, the Examiner's argument that new transcription factor binding sites are constantly discovered does not render the broad term indefinite. Just as we would not find the word "adhesive" to be indefinite because new types of glue are constantly being discovered, we do not find the phrase transcription factor binding sites indefinite.

We reverse the indefiniteness rejection of claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96.

B. 35 U.S.C. § 112, first paragraph enablement rejection

The Examiner contends that the Specification
does not reasonably provide enablement for any variant
DNA molecules encoding any reporter polypeptide having
at least 90% identity to any wild type reporter polypeptide

or any chloramphenicol acetyltransferase, *Renilla* luciferase, beetle luciferase, beta-lactamase or beta-galactosidase and having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences than a mammalian codon optimized version of the parent nucleic acid.

(Ans. 10.)

Appellants argue that

One skilled in the art, having read Appellant's specification, would know how to make and use one or more synthetic nucleic acid molecules encoding a chloramphenicol acetyltransferase, beetle or *Renilla* luciferase, beta-lactamase, beta-glucuronidase or beta-galactosidase that may not be identical in amino acid sequence, but has at least 90% identity, to a reporter polypeptide.

(App. Br. 24.) Appellants contend that “Appellant's specification describes altering the structure of a parent reporter nucleic acid sequence by iterative codon replacement to reduce TFBS, intron splice sites, poly(A) addition sites, and prokaryotic 5' noncoding regulatory sequences” (App. Br. 25).

Appellants point out that because the outcome of a “a screening program may be unpredictable is precisely why a screening program is carried out. It simply cannot reasonably be contended that a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance” (App. Br. 27).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Would it have required undue experimentation to identify nucleic acid molecules encoding reporter molecules which have a reduced number of mammalian transcription factor coding sequences?

Findings of Fact (FF)

Breadth of the Claims

1. “The rejected claims are not limited to any particular chloramphenicol acetyltransferase, beetle luciferase, beta-lactamase or beta-galactosidase” (Ans. 27).

2. Claim 1 requires that the nucleic acid differ from the wild type reporter gene sequences by at least 25% (*see* Claim 1).

Presence of Working Examples

3. The Specification discloses several working examples of optimized genes (*see, e.g.,* Spec. 73-74, Tables 11 and 12).

Amount of Direction or Guidance Presented

4. The Specification teaches a process of assigning preferred codons to each amino acid in a target molecule, e.g., a native nucleotide sequence, based on codon usage in a particular species, identifying potential transcription regulatory sequences such as transcription factor binding sites in the nucleic acid sequence having preferred codons, e.g., using a database of such binding sites, optionally identifying other undesirable sequences, and substituting an alternative codon (i.e., encoding the same amino acid) at positions where undesirable transcription factor binding sites or other sequences occur.

(Spec. 37:17-24.)

5. The Specification teaches

[u]sing YG #81-6G01 as a parent gene, two synthetic gene sequences were designed. One codes for a luciferase emitting green luminescence (GR) and one for a luciferase emitting red luminescence (RD). Both genes were designed to 1) have optimized codon usage for expression in mammalian cells, 2) have a reduced number of transcriptional regulatory sites including mammalian transcription factor binding sites, splice sites, poly(A) addition sites and promoters, as well as prokaryotic (*E. coli*) regulatory sites, 3) be devoid of unwanted restriction sites, e.g., those which are likely to interfere with standard cloning procedures, and 4) have a low DNA sequence identity compared to each other in order to minimize genetic rearrangements when both are present inside the same cell.

(Spec. 44:4-13.)

6. The Specification teaches that the “following priority was established for reduction of transcriptional regulatory sites: elimination of transcription factor (TF) binding sites received the highest priority, followed by elimination of splice sites and poly(A) addition sites, and finally prokaryotic regulatory sites” (Spec. 44:17-20).

7. The Specification discloses specific software and databases to identify and remove splice sites, poly(A) addition sites and prokaryotic regulatory sites (*see* Spec. 47-49).

8. The Specification teaches “[t]o check for the presence, location and identity of potential TF [transcription factor] binding sites, the sequences of both synthetic genes were used as query sequences to search a database of transcription factor binding sites (TRANSFAC v3.2).” (Spec 49:27-29.)

State of the Prior Art and Unpredictability of the Art

9. The Examiner relies upon Hastings, Wood (1995) and Wood (1989) to find that “[a]ll of these disclosures clearly highlight that the diversity of luciferases as a group is very high and even the beetle luciferases are very diverse such that art guidance with regard to making variants of one or more of these specific genes would not likely be useful for making variants” (Ans. 30).

10. Wood (99/14336) discloses a recursive methods which “include directed evolution using a polynucleotide sequence encoding a first beetle luciferase as a starting (parent) sequence, to produce a polynucleotide sequence encoding a second luciferase with increased thermostability” (Wood (99/14336) 3:12-15).

11. Appellants note that “with regard to luciferases, numerous substitutions have been identified in or introduced into beetle luciferases without affecting the reporter property of the substitution variants (see, e.g., Kajiyama et al., Protein Engineering, 4:691 (1991)), Wood et al., J. Biolumin., 4:31 (1989), Wood et al., J. Biolumin., 5:107 (1990) and Sala-Newby et al., Biochem. J., 279:727 (1991)), U.S. Patent Nos. 5,670,356, and 6,602,677” (App. Br. 26).

12. Zhang¹ teaches that “[s]tarting with known natural protein(s), multiple rounds of mutagenesis, functional screening, and amplification can be carried out. When the mutation rate, library size, and selection pressures

¹ Ji-Hu Zhang et al., *Directed evolution of a fucosidase from a galactosidase by DNA shuffling and screening*, 94 PROC. NAT’L ACAD. SCI. 4504-4509 (1997).

are properly balanced, the desired phenotype of a protein generally increases with each round (1-8). The advantage of such a process is that it can be used to rapidly evolve any protein, without any knowledge of its structure” (Zhang 4504, col. 1).

13. Sherf teaches modification of luciferase to permit “removal of potentially genetic regulatory sites and inconvenient endonuclease restriction sites from within the gene, and improvement of the codon usage for mammalian and plant cells” (Sherf, col. 2, ll. 61-64).

Quantity of Experimentation necessary

14. The Examiner finds that a “skilled artisan would be well aware that as the number of modifications increases the number of possible sequences **increases** exponentially while the number of active sequences **decreases** exponentially” (Ans. 32).

15. Appellants state that the “as of Appellant’s effective filing date it was well within the skill of the art worker to screen libraries encoding variant reporter protein sequences” and Appellants quote the Examiner’s Office Action from January 6, 2004, where “the Examiner commented that ‘a skilled artisan could easily determine if any variant retained the function of the parent nucleic acid’” (Reply Br. 9).

Discussion of 35 U.S.C. § 112, first paragraph Enablement rejection

“The essential question here is whether the scope of enablement ... is as broad as the scope of the claim[s].” *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991).

We agree with the Appellants that the Examiner has not provided sufficient evidence to show that it would have required undue experimentation to practice of the full scope of the claimed invention.

We note that while the claims are relatively broad (FF 1-2), Appellants outline the steps required to prepare the claimed synthetic nucleic acid molecule and exemplify making the claimed molecules (FF 3-8). “It is undisputed that by 1988 those skilled in the art knew several techniques for altering genetic sequences, including deletion and point mutations.” *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1070 (Fed. Cir. 2005). Further, the Zolotukhin, Sherf, Donnelly, Pan, Cornelissen, and Hey references, relied on by the Examiner appear to run counter to the Examiner’s assertion that undue experimentation would be required on this record.

“Enablement is not precluded by the necessity for some experimentation such as routine screening.” *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). The evidence shows that while luciferases may be a diverse group of enzymes (FF 9), the recursive screening methods were routine to effect changes that even altered enzyme specificity with routine experimentation (FF 10-15).

In sum, the Examiner failed to provide an evidentiary basis to support a conclusion that it would require undue experimentation to make and screen any or all mutations within the scope of the claimed invention. The mere fact that additional experimentation is necessary does not mandate a conclusion that such experimentation would have been considered to be “undue” in this art.

The Examiner has also failed to provide an evidentiary basis to support a conclusion that once made; a person of ordinary skill in the art would not be able to use a claimed nucleic acid that falls within the scope of Appellants' claimed invention. Here, as in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), we find no evidence to support the Examiner's assertion that undue experimentation will be required by those skilled in the art to practice Appellants' claimed invention.

For the foregoing reasons, we reverse the rejection of claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-33, 35-39, 41-45, 60, 67, 69, 70, 81, 86, 88 and 90-95 under the enablement provision of 35 U.S.C. § 112, first paragraph.

C. 35 U.S.C. § 103(a) rejection over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, and Hey

The Examiner argues that

it would have been obvious to further modify the luciferase gene of Sherf et al. to both increase the codon preference for humans as each of Zolotukhin et al., Donnelly et al., Pan et al. and Hey et al. each teach modifying a large percentage of the codons of a gene to be expressed in a host of interest and to remove potential promoter sequences, transcription binding factor sites, polyadenylation sites and splice sites as each of Sherf et al., Donnelly et al., Pan et al., Cornelissen et al. and Hey et al. each teach modifying at least several

codons of a gene to be expressed in a desired host cell to match the codon preference of the host cell and/or to eliminate undesired sequences in order to increase its expression in the desired host cell

(Ans. 17-18).

Appellants argue that the “combination of references does not disclose or suggest Appellant’s invention as each reference discloses a different way to modify the coding sequence of a different gene to increase expression, i.e., viral genes, a gene from a parasite associated with malaria, an insect toxin gene, a storage protein gene, or a reporter gene” (App. Br. 36). Appellants also argue that “the problem in the art (improved expression of genes in heterologous systems) has been ‘solved’ by each of the cited documents (in different ways) and so one of skill in the art would not look to combining the references in a particular way in the absence of Appellant’s disclosure” (App. Br. 38).

Appellants further contend that “one of ordinary skill in the art in possession of the cited art would have no reasonable expectation that any particular set of changes may improve activity or be otherwise desirable in a gene that is to be expressed in a highly evolutionarily distinct cell” (App. Br. 40).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Would it have been obvious to an ordinary artisan to prepare synthetic nucleic acids which are optimized for expression using the teachings of Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, and Hey?

Findings of Fact

16. Zolotukhin teaches “synthetic and ‘humanized’ versions of green fluorescent protein (GFP) genes adapted for high level expression in mammalian cells, especially those of human origin” (Zolotukhin, Abstract).

17. Zolotukhin teaches “humanized genes ... definable by genes in which at least about 10% of said codon positions contain a humanized codon. That is, they contain a codon that is preferentially used in human genes in place of a codon that is not so frequently used in human genes” (Zolotukhin, col. 2, ll. 63-67).

18. Zolotukhin teaches humanized genes that have at least “25%, about 30% or about 35% of the codon positions defined by the presence of a humanized codon” (Zolotukhin, col. 3, ll. 1-4). Zolotukhin also contemplates “[h]umanized gfp genes wherein at least about 50% or above of the codon positions contain a humanized codon” (*id.* at ll. 5-7).

19. Sherf teaches “[a] modified form of beetle luciferase, which has been engineered for improved genetic reporting” (Sherf, Abstract).

20. Sherf teaches the removal of “potentially interfering restriction sites and genetic regulatory sites from the gene, [and the] improvement of the codon usage for mammalian cells” (Sherf, Abstract).

21. Sherf discloses the elimination of sequences which encode transcription factor binding sites for known mammalian transcription factors including ATF, AP1, Sp1, AP2, etc. which would interfere with its genetically neutral behavior (Sherf, col. 3-5).

22. Sherf teaches the removal of “[t]hree palindromic sequences which could spuriously affect expression” (Sherf, col. 9, ll. 9-11).

23. Donnelly discloses a modified hepatitis C virus core antigen gene wherein the gene is optimized for human host cell codon usage, and also eliminates sequences which encode for undesired sequences (such as ATTTA sequences, intron splice sites, etc.) (*see* Donnelly 17-18).

24. Pan discloses a modified *Plasmodium falciparum* gene in which the codons are optimized for human host cells and sequences which might be detrimental to transcription (such as promoter sequences, intron splice sites and long runs of purines which might act as transcriptional termination sequences) are eliminated (*see* Pan 1095, col. 1; Pan 1096, col. 2).

25. Cornelissen discloses a modified *Bacillus thuringiensis* gene in which the codons are altered to eliminate sequences which, inter alia, might be detrimental to transcription including cryptic promoters or DNA regulatory elements (*see* Cornelissen, col. 9, ll. 10-25, col. 10, ll. 8-31).

26. Hey discloses a plant sink protein gene in which the codons are optimized for plant host cells and wherein sequences which might be detrimental to transcription (including promoters, transcription factor binding sequences, intron splice sites, transcriptional termination sequences and runs of 4 or more pyrimidines which might interfere with transcription) are eliminated (*see* Hey, col. 9, l. 35 to col. 12, l. 3).

Discussion of 35 U.S.C. § 103(a) over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, and Hey

Zolotukhin teaches the modification of fluorescent proteins including GFP by modifying the codons (FF 16-18) and Sherf teaches removal of unwanted sites which interfere with expression (FF 19-22). Donnelly, Pan, Cornelissen, and Hey all teach removal of sites which interfere with

expression, including intron splice sites, transcription factor binding sites, and prokaryotic regulatory sequences (FF 23-26). We conclude that the Examiner has set forth a prima facie case that claim 1 would have been obvious to the ordinary artisan in view of Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, and Hey.

Appellants argue that “the problem in the art (improved expression of genes in heterologous systems) has been ‘solved’ by each of the cited documents (in different ways) and so one of skill in the art would not look to combining the references in a particular way in the absence of Appellant’s disclosure” (App. Br. 38). In *KSR*, the Supreme Court indicated that “[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). The evidence of record (FF 16-26) demonstrates that Appellants combination is a predictable application of the prior art methods to remove unwanted sequences which interfere with expression.

We recognize Appellants’ assertion that Cornelissen teaches that because only a relatively small number of modifications result in a substantial increase of foreign gene expression in plants, the modified genes produced in accordance with their invention are unlikely to contain newly introduced sequences that interfere themselves with expression of the gene in a plant cell environment (column 13, lines 37-42).

(App. Br. 36.) We are not persuaded. Cornelissen teaches that bacterial genes, particularly BT ICP genes, may contain cis-acting regulatory

elements in their coding regions “that seriously hamper the expression of these genes when they are introduced, under control of appropriate plant regulatory sequences ... in a plant cell environment” (Cornelissen, col. 13, ll. 27-31). In this regard, Cornelissen teaches that “[i]n general less than about 10% ... nucleotide modifications in the coding region are required in order to substantially alleviate the expression problem” (Cornelissen, col. 13, ll. 33-36). Accordingly, while Cornelissen teaches the need to alter regulatory elements in a target gene to avoid expression problems; Cornelissen generalizes on the amount of modification necessary to substantially alleviate the problem associated with the expression of bacterial genes in a plant environment.

Contrary to Appellants’ assertion, we do not find that Cornelissen is opposite to those of the claimed invention (*see* App. Br. 36). A reference is said to “teach away” from a claimed invention when it “suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant” (*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). We do not find and Appellants have not identified a teaching in Cornelissen that would suggest that a modification of more than 10% of the coding regions of a target nucleic acid should be avoided or that a modification of less than 10% of the coding region completely alleviates the expression problem. Instead, we find only a generalized teaching that for bacterial genes, particularly BT ICP genes, the modification of less than about 10% of the coding region may be sufficient to substantially alleviate the expression problem. For the foregoing reasons we do not find that Cornelissen teaches away from Appellants’ claimed invention.

Appellants argue that none of the cited references teaches the use of software to identify mammalian transcription factor binding sites as required by claim 90 (*see* Ans. 40). However, Sherf teaches that “the luciferase gene sequence was scanned using a database of consensus sequences for transcription factor binding sites” (Sherf, col. 8, ll. 65-67). Pan clearly uses software for screening for undesirable sites, teaching “[a]ll analysis programs mentioned below were from the Genetics Computer Group program collection. . . . ‘Find Patterns’ was used to search for consensus sequences that are indicative of prokaryotic promoters, poly(A) signals and exon-intron boundaries. . . . All these structures, when encountered, were eliminated by using alternative codons” (Pan 1095, col. 1).

Further, we agree with the Examiner that since claims 90, 95 and 96 are product by process claims, “[a] nucleic acid in which the sites to be removed were identified by an undefined computer program would not differ in any respect from a nucleic acid in which the sites to be removed were identified by any other method” (Ans. 44). *See In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985)(citation omitted)(“The patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.”)

We are also not persuaded by Appellants’ arguments regarding “the ‘obvious-to-try’ standard” (App. Br. 41).

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good

reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 127 S. Ct. at 1742.

We affirm the rejection of claims 1 and 90 under 35 U.S.C. § 103(a). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejections of claims 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86, and 91-95 as these claims were not argued separately.

D. 35 U.S.C. § 103(a) rejection over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey and Wood (WO 99/14336)

Appellants repeat the arguments addressed above, and further argue that “none of the cited documents discloses or suggests a synthetic nucleic acid molecule comprising SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 297, or a nucleic acid molecule which is capable of hybridizing thereto under high stringency conditions” (App. Br. 46).

The Examiner contends that “Wood et al. clearly disclose nucleic acids encoding wild-type LucPpLYG, a luciferase having 100% identity to SEQ ID NO: 23 and 97% identity to the protein encoded by SEQ ID NO: 2.” (Ans. 61.) The Examiner argues that

[f]ollowing the suggestions of Zolotukhin et al. with regard to specific codon optimization choices for high level expression in human cells followed by modifications to eliminate undesirable sequences as taught by the secondary references, while not leading a skilled artisan to the specific nucleotide sequence of SEQ ID NO:9, SEQ ID NO:7, SEQ

ID NO:8, SEQ ID NO:18, SEQ ID NO:297, or SEQ ID NO:301 (as this would require that the art suggest all of applicants specific modification choices) would lead a skilled artisan to produce a optimized sequence which would hybridize to SEQ ID NO:9 under high stringency conditions as high stringency hybridization conditions still allow for a substantial number of positions (i.e., up to approximately 5% of the total; i.e., approximately 81 nucleotides in this case) in which the individual choices could be different.

(Ans. 61-62.)

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Would it have been obvious to an ordinary artisan to prepare synthetic nucleic acids which hybridize to SEQ ID Nos listed in claim 18 using the teachings of Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey, and Wood (WO 99/14336)?

Findings of Fact

27. Wood (WO 99/14336) teaches a luciferase sequence “having 100% identity to SEQ ID NO: 23 and 97% identity to the protein encoded by SEQ ID NO: 2” (Ans. 61).

Discussion of 35 U.S.C. § 103(a) over Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey, and Wood (WO 99/14336)

The Examiner’s position that the synthetic nucleic acid of Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey, and Wood would be capable of hybridizing to the claimed SEQ ID NOs has specific basis in the disclosure of Wood that the starting material is 100% identical to a wildtype starting sequence (FF 27). Therefore, the Examiner established a prima facie case of unpatentability at least based on inherency, thereby shifting to

Appellants the burden of proving that the synthetic nucleic acid of Sherf, Zolotukhin, Donnelly, Pan, Cornelissen, Hey, and Wood would not have met the hybridization requirement. *See In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)(“Whether the rejection is based on ‘inherency’ under 35 U.S.C. § 102, on ‘prima facie obviousness’ under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products”). On this record, Appellants have proffered no such proof. The Examiner’s Final Office Action served to place Appellants on notice that they needed “to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.” *Best*, 562 F.2d at 1255. Appellants did not meet this burden of production.

We affirm the rejection of claim 18 under 35 U.S.C. § 103(a). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejections of claims 47, 71, 74, 76-78, 80, 82-85, 87, 88, and 96 as these claims were not argued separately.

E. Double patenting rejection

The Examiner finds that “[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other” (Final Rejection 17). Appellants have not addressed this rejection in their Appeal Brief.

Accordingly, we summarily affirm the rejection of claims 91, 93, and 94 under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 and 58-60 of copending Application No. 10/314,827.

CONCLUSION

In summary, we reverse the indefiniteness rejection of claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96. We reverse the rejection of claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-33, 35-39, 41-45, 60, 67, 69, 70, 81, 86, 88 and 90-95 under the enablement provision of 35 U.S.C. § 112, first paragraph.

We affirm the rejection of claims 1 and 90 under 35 U.S.C. § 103(a). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejections of claims 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86, and 91-95 as these claims were not argued separately. We affirm the rejection of claim 18 under 35 U.S.C. § 103(a). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejections of claims 47, 71, 74, 76-78, 80, 82-85, 87, 88, and 96 as these claims were not argued separately. We summarily affirm the rejection of claims 91, 93, and 94 under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 and 58-60 of copending Application No. 10/314,827

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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